

CASE REPORT

A case of new-onset cardiomyopathy and ventricular tachycardia in a patient receiving ibrutinib for relapsed mantle cell lymphoma

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Key Clinical Message

Ibrutinib is a first-in-class inhibitor of Bruton's tyrosine kinase, which is approved for use in chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom's macroglobulinemia. Although ibrutinib has been linked to an increased incidence of atrial fibrillation, this is the first report of an association with nonischemic cardiomyopathy and ventricular arrhythmia.

Keywords

Arrhythmia, cardiomyopathy, ibrutinib, mantle cell lymphoma, tyrosine kinase inhibitor

Ibrutinib is a novel, first-in-class oral Bruton's tyrosine kinase (BTK) inhibitor, approved by the United States Food and Drug Administration (FDA) for relapsed and refractory mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and Waldenstrom's macroglobulinemia [1]. Clinical trials of ibrutinib have shown good activity in patients with relapsed MCL, with phase III data showing better tolerability and improvements in progression-free survival (14.6 months on ibrutinib vs. 6.2 months with temsirolimus) [2]. Thus far, the only significant cardiac adverse events (AEs) reported have been grade 1–2 hypertension (observed in 18–29% of clinical trial patients) and atrial fibrillation (grade 3 or higher toxicity observed in 4% of patients on ibrutinib as compared to 1% on temsirolimus in the aforementioned phase III study) [1, 2]. Herein, we describe the case of a patient we treated with ibrutinib for relapsed MCL who developed left ventricular (LV) dysfunction approximately 4 months after initiating ibrutinib therapy and was subsequently hospitalized with a ventricular arrhythmia and worsened cardiomyopathy just over 1 year after starting this novel agent. To our

knowledge, this is the first report of cardiomyopathy or ventricular arrhythmia associated with ibrutinib.

Our patient is a 78-year-old gentleman with a history of MCL, which was initially diagnosed in May 2012, with his disease manifesting as a 3.5 cm right axillary mass with concomitant bone marrow involvement. His past medical history is significant for hypertension, hyperlipidemia, paroxysmal atrial fibrillation with slow ventricular response (for which a pacemaker was placed), right bundle branch block, abdominal aortic aneurysm, a remote 30 pack-year history of smoking, and gout. His initial chemotherapeutic regimen included eight cycles of R-CHOP, which he completed in October 2012, followed by maintenance rituximab from January through December 2013. He achieved complete remission (CR) on this therapy; however, in March 2014, his disease relapsed and, thus, ibrutinib was initiated at a dose of 560 mg daily, with which our patient again achieved CR.

Prior to the diagnosis of MCL, transthoracic echocardiogram (TTE) in June 2006 showed an ejection fraction (EF) of 69% with mild left atrial dilatation, mild

polyvalvular regurgitation, and mild concentric left ventricular hypertrophy (LVH). A repeat TTE performed just after completing R-CHOP in December 2012 was essentially unchanged, with an EF of 65% and similar mild structural findings. However, just 4 months after starting ibrutinib, in July 2014, a routine TTE revealed an EF of 45% with mild global hypokinesis and mild concentric LVH. His medications at this time included ibrutinib, lisinopril, low-dose aspirin, and allopurinol.

In May 2015, our patient presented to an outside hospital with malaise, where he was found to have ventricular tachycardia with a heart rate in the 180s, which resolved after administration of procainamide, and was subsequently managed with amiodarone. He was noted to have an elevated troponin I at the time of admission, which peaked at 3.83 and subsequently downtrended. A coronary angiogram was performed, revealing three-vessel nonobstructive coronary artery disease (CAD) and severe left ventricular dysfunction out of proportion to his CAD. A TTE showed an EF of 41%, moderate left ventricular enlargement, and global hypokinesis. A cardiac MRI was also performed, which was in agreement with this TTE and showed no signs of myocardial scarring.

Given that our patient's depressed EF was first noted 4 months after the initiation of ibrutinib and that the addition of ibrutinib was the only medication change made in the preceding year, this agent was discontinued and replaced with combination rituximab and lenalidomide therapy. After discharge, oral amiodarone and warfarin were added to our patient's medication regimen. A repeat TTE in December 2015 showed significant improvement in the previously observed cardiomyopathy, with an EF of 60%, mild LV dilatation, and mild mitral and aortic regurgitation. The prompt improvement in cardiac function and lack of arrhythmias after cessation of ibrutinib raises the question as to whether ibrutinib itself may have played a causative role in our patient's presentation.

Tyrosine kinases (TKs) are enzymes that play an important role in growth factor signaling, both in normal and malignant cells. A wide array of monoclonal antibody and small molecule tyrosine kinase inhibitors (TKIs) have been developed over the last 20 years and many more are currently under investigation [3]. Cardiac toxicity in the form of systolic dysfunction and resultant heart failure has been reported with a number of the TKIs, including trastuzumab, bevacizumab, sunitinib, dasatinib, nilotinib, and imatinib. It is thought that cardiac injury results because the same pathways that allow for pathologic survival or abnormal proliferation of malignant cells may also be involved in the survival and function of normal cells, such as cardiomyocytes [4].

Overall, it appears that ibrutinib has a high specificity for the BTK receptor, meaning that relatively little off-

target toxicity would be expected, and clinical trial data have thus far supported the tolerability and relative safety of this novel drug [1]. Clinical trial data have only been revealing of two major cardiac AEs thus far, hypertension and atrial fibrillation [1, 2]. In phase III testing of ibrutinib versus temsirolimus for relapsed or refractory MCL, grade 3 or higher atrial fibrillation was noted in 4% of patients on ibrutinib as compared to 1% on temsirolimus [2]. It has been hypothesized that the increased risk of atrial fibrillation associated with ibrutinib may be related to on-target toxicity to the phosphoinositide 3-kinase (PI3K)–Akt pathway in cardiomyocytes. The PI3K–Akt pathway typically regulates cardiac protection in stressful conditions and is also thought to play an important role in the prevention of stress-induced cardiomyopathy [5]. This case represents the first report of cardiomyopathy and ventricular arrhythmia associated with ibrutinib. Our patient had a history of treatment with the cardiotoxic anthracycline, doxorubicin; however, prior to initiation of ibrutinib, his cardiac function was essentially normal, worsened 4 months after beginning treatment, and then rapidly resolved almost completely, arguing against an anthracycline effect. Thus, we suggest that, given the older age of most patients with CLL and MCL, further surveillance studies should explore ibrutinib-related cardiomyopathy and ventricular arrhythmia and potential explanatory pathways.

Conflict of Interest

None declared.

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